3D-Spheroid Culture of Human Gingiva-Derived Mesenchymal Stem Cells Enhances Mitigation of Chemotherapy-Induced Oral Mucositis.

Journal: Stem Cells Dev

Publication Year: 2011

Authors: Q Zhang, A L Nguyen, S Shi, C Hill, Smith P Wilder, T Krasieva, A D Le

PubMed link: 21689066

Funding Grants: Oral and Craniofacial Reconstruction Using Mesenchymal Stem Cells

Public Summary:
Mesenchymal stem cells (MSCs) derived from adult tissues represent a heterogeneous subset of stromal cells that proliferate in vitro as plastic-adherent cells, capable of colony formation, multi-lineage differentiation, immunomodulatory, and anti-inflammatory functions. MSCs possess the ability to home and engraft at the injured site and promote tissue repair through synergistic downregulation of proinflammatory cytokines and increased production of a myriad of soluble factors with antioxidant, antiapoptotic, and proangiogenic functions. As such, MSC-based therapy plays a promising therapeutic modality for tissue regeneration and wound repair; despite numerous potentials, several limitations remain, including unpredictable engraftment, survival, and biological functions ofMSCs at the injury sites. To date, several strategies have been reported for optimizing the functions of MSCs, including genetic modifications and in vitro priming with proinflammatory ytokines (such as IFN-g or TNF-a), or manipulation of culture conditions. For instance, several studies have reported that aggregation of MSCs in a short-term 3D spheroid culture can significantly enhance their multipotent differentiation, anti-inflammatory properties, proangiogenic ability, and engraftment at the ischemic environment. We report here a 3D spheroid culture approach to optimize stem cell properties and therapeutic effects of human gingiva-derived mesenchymal stem cells (GMSCs) in mitigation of experimental oral mucositis. Under growth condition of ultra-low attachment, GMSCs spontaneously aggregated into 3D spheroids and exhibited distinct early stem cell phenotype characterized by elevated expression Stro-1 and CXC chemokine receptor 4 (CXCR-4) as well as OCT-4 and Nanog, 2 important transcriptional factors relevant to stem cell properties, and decreased expression of MSC-associated markers, including CD29, CD90, and CD105. Functionally, spheroid GMSCs are capable of enhanced multipotency and augmented secretion of several chemokines and cytokines relevant to cell migration, survival, and angiogenesis. More importantly, spheroid GMSCs expressed increased levels of reactive oxygen species, hypoxia-inducible factor (HIF)-1 and -2α, and manganese superoxide dismutase, which correlated with improved resistance to oxidative stress-induced apoptosis. Using an in vivo murine model of chemotherapy-induced oral mucositis, we demonstrated that spheroid-derived GMSCs possessed better therapeutic efficacy than their adherent cells in reversing body weight loss and promoting the regeneration of disrupted epithelial lining of the mucositic tongues. These findings suggest that 3D spheroid culture allows early stemness preservation and potentially precondition GMSCs for enhanced mitigation of oral mucositis.

Scientific Abstract:
Mesenchymal stem cells (MSCs) are capable of regenerative and immunomodulatory functions in cell based therapies in a variety of human diseases and injuries; however, their therapeutic efficacy and potential side effects remain major obstacles in clinical applications. We report here a 3D-spheroid culture approach to optimize stem cell properties and therapeutic effects of human gingiva-derived mesenchymal stem cells (GMSCs) in mitigation of experimental oral mucositis. Under growth condition of ultra-low attachment, GMSCs spontaneously aggregated into 3D-spheroids and exhibited distinct early stem cell phenotype characterized by elevated expression Stro-1 and CXCR-4 as well as OCT-4 and Nanog, two important transcriptional factors relevant to stem cell properties, and decreased expression of MSC associated markers, including CD29, CD90 and CD105. Functionally, spheroid GMSCs are capable of enhanced multipotency and augmented secretion of several chemokines and cytokines relevant to cell migration, survival and angiogenesis. More importantly, spheroid GMSCs expressed increased levels of reactive oxygen species (ROS), HIF-1 and -2alpha, and manganese super-oxidative dismutase (MnSOD), which correlated with improved resistance to oxidative stress-induced apoptosis. Using an in vivo murine model of chemotherapy-induced oral mucositis, we demonstrated that spheroid-derived GMSCs possessed better therapeutic efficacy than their adherent cells in reversing body weight loss and promoting the regeneration of disrupted epithelial lining of the mucositic tongues. These findings suggest that 3D-spheroid culture allows early stemness preservation and potentially precondition GMSCs for enhanced mitigation of oral mucositis.

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